REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested.

Status of the Claims

Claims 5-18 and 23-32 were acted on by the Examiner. Claims 7, 9, 10, 26 and 28 have been amended. Claims 5-18 and 23-32 are presented for examination.

Claim 7 has been amended to correct the spelling of Creutzfeldt-Jacob syndrome. Claims 9 and 10 have been amended to correct the lack of antecedent basis for the term "pharmaceutical." Claim 26 has been amended to recite that the immunosuppressant is administered "in an amount such that the level of said transgenic product, as measured 15 days following the discontinuation of said administration of said immunosuppressant, is at least 50% greater than the level of said product when said immunosuppressant is not administered." Claim 28 has been amended to depend on Claim 26 rather than Claim 16.

A. Section 102(a) Rejections of Claims 26 and 27

Claims 26 and 27, directed to a method for increasing the tolerance of a mammal to transgenic cells, were rejected by the Examiner under 35 U.S.C. §102(a) as being anticipated by the disclosure of Smith et al., *Gene Therapy* (1996); 3:496-502 (Abstract only) (hereafter "Smith et al.") and, alternatively, by the disclosure of Trapnell et al., International Publication No. WO 96/12406 (hereafter "Trapnell et al.").

Smith et al. (abstract only) is directed to a method of administering adenovirus vectors expressing a transgene along with administration of an immunosuppressant that will decrease the formation of anti-adenovirus neutralizing antibody to allow for a more effective second administration of an adenovirus vector.

Trapnell et al. is directed to a method of gene therapy involving the concurrent and repeated administration of a therapeutic gene of interest via an adenoviral vector and an immunosuppressive agent, such as DSG, for the suppression of the humoral immune response. Trapnell et al. is concerned with the repeated administration of an adenoviral vector and the resultant humoral immune response.

Claim 26 has been amended to recite that the immunosuppressant is administered "in an amount such that the level of said transgenic product, as measured 15 days following the discontinuation of said administration of said immunosuppressant, is at least 50% greater than the level of said product when said immunosuppressant is not administered." Claim 27 depends on Claim 26. Claim 28 has been amended to depend from Claim 26. Support for the amendment of Claim 26 can be found in Example 2, particularly Table 1 which compares, among other things, the levels of α1-antitrypsin of the control group (which received no immunosuppressant) and the DSG group (which received 5 days of DSG administration) for a period of 200 days following administration of the adenoviruses. Table 1 clearly shows the desired lasting effect of DSG on the expression of the transgenic product.

This amendment to Claim 26, from which Claims 27 and 28 depend, overcomes each of the Examiner's Section 102(a) rejections. For a reference to anticipate a claim the reference must disclose each element of the invention as defined by the claim. Each of Claims 26, 27 and 28 recite a method for increasing the tolerance of a mammal to transgenic cells which comprises the step of administering to said mammal during said therapy an immunosuppressant in an amount such that the level of the expressed product of said transgene, 5 days following the discontinuation of said therapy, is at least 50% greater than the level of said product when said pharmaceutical is not administered. Neither Smith et al. nor Trapnell el al. disclose administering an immunosuppressant such that the transgenic product five days following the discontinuation of therapy is at least 50% greater than the level of said product when said immunosuppressant is not administered. Rather, both Smith et al. and Trapnell et al. are directed to repeated administrations of an adenoviral vector. Accordingly, this rejection should be withdrawn.

B. Double Patenting Rejection of Claim 25

The Examiner has asserted a statutory double patenting rejection of Claim 25 as being a substantial duplicate of Claim 28 and thus objectionable due to statutory type double patenting. Claims 25 and 28 previously both depended on Claim 16.

Claim 28 has been amended to depend from Claim 26, and thus, the Examiner's statutory double patenting rejection is no longer applicable and should be withdrawn.

C. Rejection of Claims 5 to18 and 23 to 32 Under 35 U.S.C. § 112, Second Paragraph

Claims 5-18 and 23-32 were rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants first note that the only maintained rejection under 35 U.S.C. § 112, second paragraph appears to be over Claims 5-18, 23-25, and 28. If this is incorrect, Applicants respectfully request clarification from the Examiner.

The Examiner has maintained the rejection of Claim 16 as being vague and indefinite because it recites the term "the improvement" without antecedent basis for the term and because it is unclear to the Examiner how an improvement can comprise administration of an immunosuppressant. Claims 5-15, 17-18, 23-25, and 28 have been rejected because they depend on Claim 16. Claim 28 has since been amended to depend from Claim 26.

Applicants' Amendment of December 30, 2003 deleted the term "the improvement" from Claim 16. Accordingly, this rejection is moot. If this is incorrect, Applicants respectfully request clarification from the Examiner.

D. Rejections of Claims 5 to 18 and 23 to 32 Under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

Claims 5-18 and 23-32 were rejected by the Examiner under the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse this rejection. Although the Examiner has very helpfully grouped the enablement issues into six categories, it is not always clear which categories apply to which claims. For purposes of this reply, Applicants will assume that the Examiner intended that each category be applied to each claim. Many of the claims, however, define subject matter that would render moot a particular enablement rejection.

Categories 1 and 5: As the Examiner has addressed categories 1 and 5 together, Applicants will do the same. The Examiner has rejected the claims as lacking enablement for

(1) "the administration of, or increasing the tolerance of, transgenic cells in any mammal including a man wherein the transgenic cells were from the same or different species[,] expressed any gene or where the method was for treating any disease by gene therapy or by *ex vivo* cell therapy" and (5) "the claimed method when transgenic cells are transplanted in a mammal or in a man, except for autologous cell transplantation which would produce minimal immune response."

Claim 16 is directed to "a method for expressing a transgenic product in a mammal comprising introducing into a cell of said mammal a transgene capable of expressing said transgenic product." Claims 5-15, 17-18, and 23-25 depend on Claim 16. With respect to Claim 16, the Examiner has recognized that this enablement rejection does not apply as Claim 16 has been amended "to read only on transgenic cells derived from the same mammal in which they are transplanted." Accordingly, it is unclear why the Examiner has specifically maintained such a rejection over dependent Claims 23-25. The rejection of Claims 23-25 should be withdrawn.

Claim 29 contains the same recitation as Claim 16 namely that the transgene is introduced into "a cell of said mammal." Claims 30-32 depend on Claim 29. As the Examiner has recognized that this rejection does not apply to Claim 16, Applicants do not understand how it could apply to Claims 29-32, and thus, respectfully request that the Examiner withdraw this rejection.

Claim 26 is directed to transgenic cells that are produced "*in vivo* after the administration of a vector." Claims 27-28 depend on Claim 26. Since the transgenic cells are produced *in vivo* after the administration of the vector, the method involves only the cells from that particular mammal and does not involve cells from other species or *ex vivo* cell therapy. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Category 2: The Examiner has rejected the claims as lacking enablement for "how transgenic cells would be prepared *in vitro* or how a transgenic cell would be administered to a mammal or what doses of the cell would be used." Applicants respectfully traverse this rejection.

With respect to Claim 16, the Examiner has recognized that this rejection does not apply. Claims 5-15, 17-18, and 23-25 depend on Claim 16. Accordingly, it is unclear why

the Examiner has specifically maintained such a rejection over dependent claims 23-25. In any event, Claim 16 and its dependent claims are enabled for the reasons discussed below with respect to Claims 29-32. Applicants respectfully request that the Examiner withdraw this rejection or provide clarification.

Claims 24 and 26 are directed to transgenic cells that are "produced *in vivo*." Claims 27-28 depend on Claim 26. Accordingly, this rejection as applied to Claims 24 and 26-28 is misplaced and should be withdrawn.

Claim 29 is directed to "a method for increasing the tolerance of a mammal to transgenic cells comprising introducing into a cell of said mammal a transgene capable of expressing said transgenic product." Claims 30-32 depend on Claim 29. Accordingly, it is unclear why the Examiner states that Claims 29-32 encompass transgenic cells from the same or different species. Moreover, these claims are enabled for a method of *in vitro* or *ex vivo* gene therapy. Gene therapy protocols are widely available and one of skill in the art would recognize that the claimed methods may be useful in *in vitro* or *ex vivo* gene therapy methods.

For example, the following articles (attached to this Reply) were published prior to the present application's priority date and describe various *in vitro* or *ex-vivo* gene therapy protocols that could be used with the claimed methods: Bunnel et al., Blood, 89:1987-95 (1997); Mesri et al., Circulation Research, 76:161-67 (1995); Sutkowski et al., Proc. Natl. Acad. Sci. USA, 91:8875-79 (1994); Mavilio et al., Blood, 83:1988-97 (1994); Lim et al., Proc. Natl. Acad. Sci. USA, 86:8892-96 (1989).

Bunnel et al. discloses a method of obtaining and isolating peripheral blood mononuclear cells (PBMC) from rhesus macaques. The PBMCs are transduced via two rounds of optimized retroviral transduction and a single round of standard transduction. The cells are then expanded and reintroduced into the rhesus macaques intravenously.

Mesri et al. discloses a method of transducing NIH 3T3 fibroblasts with a replication-defective herpes simplex virus type 1 (HSV-1) amplicon vector. The fibroblasts were transduced with an HSV-1 vector expressing human vascular endothelial growth factor (VEGF), resuspended in basement memberane extract, and injected subcutaneously into syngeneic C57BL/6 mice. A Western blot assay shows a marked expression of VEGF at the second and seventh day after the subcutaneous injection.

Sutkowski et al. discloses an animal model system for somatic cell gene therapy using

primary B lymphocytes. The B lymphocytes are obtained from 6 to 9 week old mice. The B lymphocytes are transduced using the Mo-MLV-based retroviral vector and injected intravenously into BALB/cBy SCID mice. Using this *ex vivo* method, Sutkowski et al. was able to express human adenosine deaminase (ADA) in the spleen of SCID mice 3 months after gene transfer.

Mavilio et al. compared "four different gene transfer protocols and different retroviral vectors designs, all carrying the same reporter gene, for their ability to infect, stable integrate, and express an exogenous gene into human lympopoietic cells." Mavilio et al. at 1995. Although differences in efficiency were observed, all the retroviral vectors could transduce the human lympopoietic cells.

Lim et al. discloses the long-term stable expression of foreign genetic sequences transferred into hematopoietic stem cells (HSCs) using retroviral vectors. Bone marrow cells are harvested from mice. The cells were transfected *in vitro* with human ADA cDNA by preincubating the cells in media containing hematopoietic growth factors and cocultivating with viral producer cells. Lim et al. report that 100% of the mice transplanted with the HSCs exhibit expression of human ADA 30 days after transplantation.

Given the examples and guidance provided in the specification, and the protocols available in the prior art, it would be a matter of routine experimentation to apply the teaching of the examples to *in vitro* or *ex vivo* gene therapy protocols. Thus, this enablement rejection should be withdrawn.

Category 3: The Examiner has withdrawn the rejection based on this issue.

Category 4: The Examiner has rejected the claims as lacking enablement for "how the methods of treatment of diabetes or AIDS, or DNA vaccination would be carried out, or what doses of the DSG would be used or what routes of administration would be used or which transgene would be used such that the effect of the transgene induced immune response is decreased by DSG treatment." Applicants respectfully traverse this rejection.

With respect to the issues regarding the treatment of particular diseases, Applicants address that issue with Category 6 below.

Claim 16 and dependent Claims 5-15, 17-18, and 23-25 are directed to "a method for

expressing a transgenic product in a mammal." Claims 26 and 29 and dependent Claims 27-28, and 30-32 are directed to "a method for increasing the tolerance of a mammal to transgenic cells."

With respect to the routes of administration and the dosage of DSG covered by the claims, Applicants note that MPEP §2164.01 states that the test of enablement requires a determination as to whether one of skill in the art can practice the claimed invention without undue experimentation. Applicants note that such is the case. The claimed invention is a method for expressing a transgenic product in a mammal and a method for increasing the tolerance of a mammal to transgenic cells. One skilled in the art, seeking to practice such a method on a certain mammal containing a certain transgene can simply use the assay described on page 8 of the application to determine which immunosuppressant to use and in what amount, what route of administration to use, and how long such an immunosuppressant should be applied.

Moreover, the specification provides examples of administering the immunosuppressants, DSG, cyclosporin A, and FK 506, intraperitoneally, at given dosages, for various periods of time. In fact the claims, themselves, define what needs to be accomplished by one of skill in the art when choosing an immunosuppressant, a dosage, and a route of administration. Whatever immunosuppressant, dosage, and route of administration is chosen, the administration of the immunosuppressant must result in a level of transgenic product, as measured 15 days following the discontinuation of the administration of the immunosuppressant, that is at least 50% greater than the level of the transgene product when the immunosuppressant is not administered. Thus, by routine experimentation, one of skill in the art by using the examples in the specification, the goal as set forth in the claims, and the knowledge in the art, would be able to determine a suitable combination of immunosuppressant, dosage, and route of administration to achieve the claimed level of transgenic product. Accordingly, practicing the claimed invention does not require undue experimentation.

As long as there is sufficient guidance to practice the claimed invention, Applicants are not required to submit information that can be determined by routine experimentation. As stated in the MPEP, section 2164.06:

"[A]n extended period of experimentation may not be undue if the skilled

> artisan is given sufficient direction or guidance." *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Any experimentation necessary to determine an effective dosage or route of administration of an immunosuppressant would be routine for one skilled in the art in view of the more than reasonable guidance provided and the extensive guidance in the scientific literature on immunosuppressant administration. It cannot be the case that Applicants after discovering the lasting effects of immunosuppressant administration on the levels of transgenic products must provide examples of administering the immunosuppressant in different dosages and by different routes of administration. Such a requirement would be unduly burdensome on applicants and would be of little to no use to one of skill in the art. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Category 6: The Examiner has rejected the claims as lacking enablement for "a method of gene therapy."

Applicants first note that Claim 16 and dependent Claims 9-12 and 17-18, and 23-25 are directed to "a method for expressing a transgenic product in a mammal." Claims 26 and 29 and dependent Claims 27-28, and 30-32 are directed to "a method for increasing the tolerance of a mammal to transgenic cells." Claims 5-8 and 13-15 are directed to the method of claim 16, wherein the transgenic cells are produced in the course of a gene therapy treatment. A gene therapy treatment, however, does not require a patient to be cured. Thus, even if a gene therapy regimen results in low expression of a therapeutically useful gene, such a low expression may still be of significant benefit to a patient, alleviating or slowing the effects of a given disease. For example, as shown in Example 2, AAT, which may be used to treat alpha-1 anti-trypsin deficiency, was shown to be expressed at increased and sustained levels after treatment with DSG.

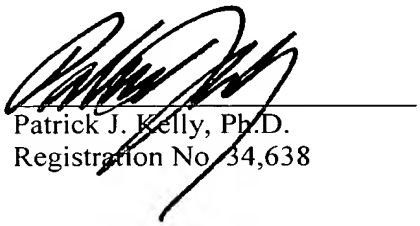
One of skill in the art would be able to apply the methods of the present application to treat other diseases. For example, one of skill in the art may follow examples 1 and 2 and

substitute different therapeutic genes for the β-galactosidase and AAT genes used in these examples with the experiment directed towards a lowered immune response and a benefit to the patient by the expression of the transgene.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

Enclosed herewith in duplicate is a Notice of Appeal. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 19-5425.

Respectfully submitted,



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